Solvent Effect as the Result of Frontier Molecular-orbital Interaction. Part 3.[1] Hetero Diels–Alder Reaction with Inverse Electron Demand between 4-Arylidenepyrazol-5-ones and Isobutyl vinyl Ether

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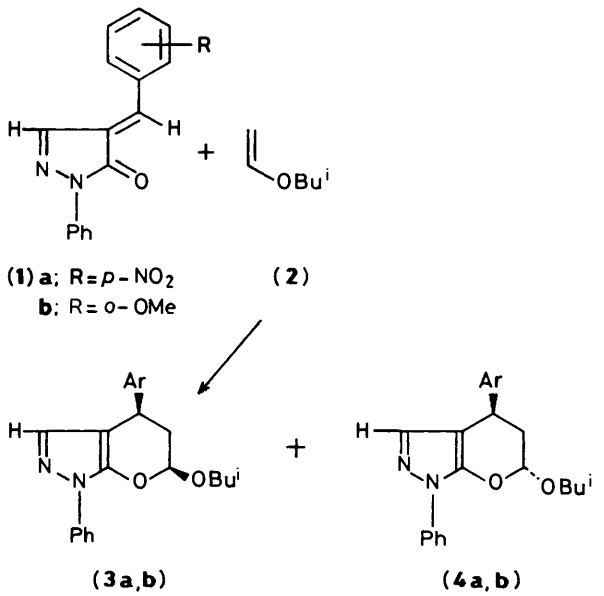
The rate of the hetero Diels–Alder reaction between 4-arylidenepyrazol-5-ones (**1a,b**) and isobutyl vinyl ether (**2**) has been determined in different solvents and a correlation between kinetic data and the solvent acceptor number has been found. This is interpreted in terms of FMO interactions between the solvent and the heterodiene which determine the LUMO energy of the solvated pyrazolones. Primary and secondary aliphatic alcohols, the high acceptor numbers of which result from their acidity due to hydrogen bonding, are also involved in significant co-ordination to the vinyl ether. This results in a negative contribution to the rate.

The stereoselectivity of the reaction between (**1a**) and (**2**) is found to be a function of the solvent and these data, and of those taken from the literature for the reaction of cyclopentadiene and methyl acrylate derivatives. This in turn suggests that in Diels–Alder reactions the solvent behaves as an electrophile which co-ordinates to either diene or dienophile, or both, depending on their MO parameters.

In the previous papers[1,2] of this series we investigated the solvent effect of the Diels–Alder (DA) reaction, with direct electron demand,[3] between 1,4-naphthoquinones and 2,3-dimethylbutadiene. The rate increased with increases in the acceptor number[4] (AN) of the solvent. The correlation between AN and the LUMO of the solvent[5] was interpreted in terms of FMO interactions between the solvent and the dienophile, which determine the LUMO energy of the solvated naphthoquinones. Thus the solvent action is not due to its physical parameters (Kirkwood function, E_T, *etc.*). If the solvent is considered to be an electrophile interacting with the dienophile, it becomes the 'third reagent' of the DA reaction acting under the control of the same parameters (FMOs) that control the reactivity of diene and dienophile.

To test the limits of this approach, which could be generally valid for cycloadditions that do not involve strongly dipolar reagents or intermediates, we investigated the solvent effect of the inverse[3] hetero-Diels–Alder (HDA) reaction between α,β-unsaturated carbonyl compounds (acting as heterodienes) and vinyl ethers.[6] The co-ordination of the solvent with the carbonyl oxygen should lower the LUMO of the heterodiene and should increase the rate as the solvent AN increases.

In this paper we report the results of the reaction between 4-(*p*-nitro)- and 4-(*o*-methoxy)benzylidene-1-phenylpyrazol-5-ones (**1a,b**) and isobutyl vinyl ether (**2**) to give a mixture of *cis*-4,6- and *trans*-4,6-4-aryl-6-isobutoxy-1-phenyl-5,6-dihydro-4*H*-pyrano[2,3-*c*]pyrazoles [(**3a,b**) and (**4a,b**) respectively, see Scheme 1]. Since the configuration of the starting pyrazoles (**1**) is *E*,[7] the *endo* transition state, stabilized by non-bonding interactions,[8] should give (**3**) as the major adducts.



Scheme 1.

Results

The kinetic runs were studied by u.v.–vis. spectroscopic analysis of the disappearing pyrazolones, at 35.7 °C to *ca.* 70% completion of reaction. In the presence of a 150–1 200-fold excess of the vinyl ether, pseudo-first-order rate constants[9] were determined and second-order rate constants were then calculated. Several solvents were tested with the obvious exception of those (*e.g.* acetic acid and 2-chloroethanol) which destroy the vinyl ether. In n.m.r. control experiments, primary and secondary alcohols appeared to react with (**2**) to give acetals, but this was found to be due to the acidity of commercial $CDCl_3$. Alcoholic solutions of (**2**) in K_2CO_3-treated $CDCl_3$ showed no side reaction between the vinyl ether and alcohols.

The kinetic data are reported in Table 1 and represent the average of at least six kinetic runs, each with varying reagent ratios. The fact that electron-attracting substituents lower the LUMO of the heterodiene explains the observation that (**1a**) reacts faster than (**1b**) by a factor of *ca.* 10. An increase in the rates by a factor of 32 for (**1a**) and 100 for (**1b**), in benzyl alcohol

Table 1. Rate constants for the reaction of (**1a,b**) and (**2**) at 35.7 °C in different solvents and values of solvent AN.

No.	Solvent	AN	$k/10^{-4}$ dm^3 mol^{-1} s^{-1} (**1a**)	(**1b**)
1	Cyclohexane	0	2.96 ± 0.08	0.26 ± 0.02
2	Mesitylene	—	3.20 ± 0.08	0.31 ± 0.005
3	*p*-Xylene	—	3.24 ± 0.03	0.32 ± 0.01
4	Toluene	—	3.93 ± 0.07	0.38 ± 0.01
5	Benzene	8.2	4.90 ± 0.09	0.45 ± 0.005
6	Carbon tetrachloride	8.6	5.9 ± 0.2	0.52 ± 0.01
7	Ethyl acetate	9.3	3.81 ± 0.06	0.32 ± 0.005
8	Diglyme	10.2	5.4 ± 0.1	0.49 ± 0.01
9	1,4-Dioxane	10.8	3.9 ± 0.1	0.42 ± 0.02
10	Fluorobenzene	—	5.14 ± 0.07	0.43 ± 0.005
11	Chlorobenzene	—	5.86 ± 0.07	0.47 ± 0.01
12	Acetone	12.5	6.3 ± 0.1	0.51 ± 0.01
13	Nitrobenzene	14.8	8.1 ± 0.3	0.60 ± 0.015
14	Benzonitrile	15.5	5.2 ± 0.3	0.68 ± 0.03
15	Nitroethane	—	9.4 ± 0.2	0.90 ± 0.01
16	Acetonitrile	18.9	10.2 ± 0.2	0.73 ± 0.01
17	Nitromethane	20.5	15.7 ± 0.2	1.24 ± 0.14
18	Chloroform	23.1	11.5 ± 0.2	1.11 ± 0.02
19	t-Pentyl alcohol	(27)[a]	51 ± 1	5.8 ± 0.2
20	t-Butyl alcohol	27.1	60 ± 1	6.4 ± 0.5
21	Cyclohexanol	(31.5)[a]	54 ± 2	10.3 ± 0.1
22	s-Butyl alcohol	(32.5)[a]	52 ± 1	8.9 ± 0.2
23	Isopropyl alcohol	33.8	39 ± 1	7.9 ± 0.3
24	Butyl alcohol	36.8	29 ± 1	8.8 ± 0.1
25	Propyl alcohol	37.3	26.5 ± 0.5	7.7 ± 0.2
26	Ethanol	37.9	26 ± 1	8.4 ± 0.3
27	Methanol	41.3	26.5 ± 0.8	14.8 ± 0.6
28	Benzyl alcohol	(50)[a]	94 ± 3	26 ± 1

[a] Values derived from the linear relationship between ANs and Taft's σ* parameters of the alkyl group of the alcohols ROH (R = Me, Et, Pr, Bu^s, Pr^i, Bu^t) (ρ = 47.8; intercept 42.4; *r* 0.99).

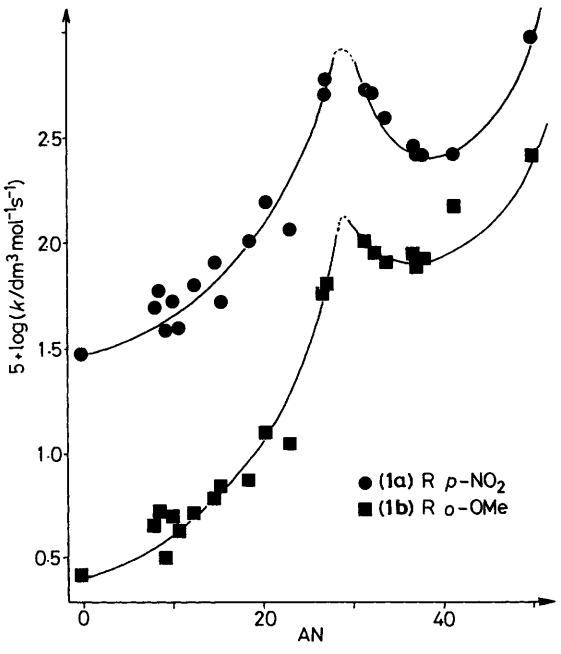


Figure 1. Rate constants for the HDA reaction between (**1a,b**) and (**2**) at 35.7 °C in different solvents, plotted *vs.* the solvent acceptor number.

compared with cyclohexane as the solvent is a notable observation. Any significant correlation was observed when log *k* was plotted *versus* either the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ or the $E_T(30)$ parameters. The former gave random points, the latter showed only an approximate correlation with protic and aprotic solvents. Even if the dipolar character of the reagents suggested a preliminary test of the polarity parameters, the significant scattering of data from linearity and either positive (**1b**) or negative (**1a**) gradient observed for protic solvents made these parameters unsuitable for rationalization of the solvent effect observed.

In order to test for a possible correlation between solvent AN and the HDA reaction rates, the ANs of some of the solvents tested, not available in the literature, were required. For alcohols, this problem was overcome by assuming a linear relationship between the ANs and Taft's σ* parameters of the alkyl group (see footnote *a* in Table 1). For aromatic solvents, the rate was found to increase with increases in the electron-attracting character of the substituents; this was as expected for solvent acting as an electrophile.

When log *k* was plotted against AN, the rates for (**1a,b**) were found to increase with the same order of increase of the AN in the cyclohexane–tertiary alcohol range and the correlations reported in Figure 1 were obtained.

Co-ordination of the solvent to the pyrazolone clearly explains the above effect. The hyperbolic shape of both curves can be derived from the relationship between the stabilization energy of the reaction and the AN given [2] by equation (1) (*a*, *b*, *c*,

$$\Delta E = \frac{a - b\,\mathrm{AN}}{c - d\,\mathrm{AN}} \qquad (1)$$

and *d* being constants), assuming that ΔE is a linear function of log *k* and hence assuming the activation entropy as constant within the series of these solvents. This had been shown in detail in a previous paper;[2] nevertheless, it was tested for (**1a, b**) in benzene and 1,4-dioxane (Table 2) and the results support the previous assumptions.

The simple model proposed cannot be used to explain the solvent effect of primary and secondary alcohols since both curves show a discontinuity. These solvents, in addition to co-ordination to the oxygen atom of pyrazolones, must induce an effect which reduces the rate constants obtained using equation (1). This effect probably arises from co-ordination to the vinyl ether.

Alcohols have the well known ability to form hydrogen bonds and this effect is quantitatively evaluated using Taft's α-scale of hydrogen-bond donor (HBD) acidities.[10] The aliphatic alcohols show decreasing HBD acidity with the increasing electron-donating character of their alkyl residue and the effect is almost proportional to the σ* values of the alkyl group.[10] The ANs of aliphatic alcohols, however, are linearly related to the σ* values of the alkyl group (Table 1, footnote *a*), hence, for this class of solvents, AN can be regarded as a measure of their HBD acidities (the linear correlation gave ρ 25.47, intercept 16.86, and *r* 0.97). The solvent, therefore, through its hydrogen bonding, again acted as an electrophile toward the vinyl ether, lowering its HOMO, and resulting in an increase in the energy separation of FMOs of heterodiene and dienophile, and a lower reaction rate.

Equation (1) alone cannot be used to represent the whole solvent effect of the HDA reactions between arylidenyl-pyrazolones and vinyl ethers. For strongly hydrogen-bonding alcohols a negative term has to be added which reduces the contribution of the first term. Since activation entropy can be assumed as constant for all solvents (see Table 2 for its values in methanol), the correlation between rate and the AN can be qualitatively understood. Even if the energy of the solvated vinyl ether can be derived by mixing the interacting orbitals of solvent

Table 2. Rates and activation parameters of HDA reactions of (**1a,b**) and (**2**) in benzene, 1,4-dioxane, and methanol.

		$k/10^{-4}$ dm^3 mol^{-1} s^{-1}		
Pyrazolones	T/°C	Benzene	1,4-Dioxane	Methanol
(**1a**)	20	2.03 ± 0.04	1.66 ± 0.06	9.9 ± 0.1
	25	2.63 ± 0.09	2.12 ± 0.09	14.0 ± 0.4
	30	3.44 ± 0.05	2.86 ± 0.03	20.2 ± 0.5
	35.7	4.9 ± 0.1	3.9 ± 0.1	26.5 ± 0.8
	$\Delta H^{\ddagger a}$	9.5 ± 0.6	9.3 ± 0.7	10.8 ± 0.4
	$\Delta S^{\ddagger b}$	−43 ± 2	−44 ± 3	−35 ± 1.5
(**1b**)	20	—	—	5.9 ± 0.15
	25	—	—	8.0 ± 0.1
	30	—	—	10.5 ± 0.2
	35.7	0.45 ± 0.05	0.42 ± 0.02	14.8 ± 0.6
	45	0.84 ± 0.3	0.81 ± 0.01	—
	55	1.52 ± 0.02	1.50 ± 0.02	—
	65	2.78 ± 0.08	2.77 ± 0.01	—
	$\Delta H^{\ddagger a}$	12.1 ± 0.9	12.5 ± 0.5	9.9 ± 0.8
	$\Delta S^{\ddagger b}$	−39 ± 2	−38 ± 1	−40 ± 2

[a] kcal mol^{-1}. [b] cal K^{-1} mol^{-1}.

and vinyl ether, a specific equation representing the shape observed requires further experimental data.*

For a quantitative evaluation of the solvent effect in both series, the curves of Figure 1 were compared. To a certain extent, the log k values for the heterodiene (**1a**) are linearly related to those of heterodiene (**1b**) (Figure 2). This occurs if primary and secondary alcohols are excluded. Since the slope is greater than 1.0, the solvent effect is slightly larger in methoxy-(**1b**) than in nitro-substituted pyrazolone (**1a**). Since the FMOs of (**1b**) are stabilized to a lesser extent than those of (**1a**), the slightly larger solvent effect observed in the former could be the result of a lower energy separation between the LUMO of the solvent and the FMOs of the heterodiene and hence the result of a large energy of interaction of these orbitals. Furthermore, the divergence from linearity of primary and secondary alcohols, with a slightly larger solvent effect observed for (**1b**), could be the result of a hydrogen-bonding co-ordination of these solvents to the substituents of the benzylidene group.[11] This could either make the arylidene group of (**1b**) less electron-releasing or the arylidene of (**1a**) less electron-attracting, hence a faster reaction for the former or a slower one for the latter.

The cis/trans *Ratio.*—Compounds (**1a,b**) should react with (**2**) to give *cis* and *trans* adducts [(**3**) and (**4**) respectively] as mentioned previously. The reaction of (**1a**) gave (**3a**) (as main adduct) and (**4a**), separable by column chromatography, the structures of which were assigned by n.m.r. spectroscopy. The reaction of (**1b**) gave (**3b**) only. In both reactions, the *endo* transition state, stabilized by non-bonding interactions, favoured the formation of the *cis* isomer.

By the use of appropriate control experiments, the product mixtures were found to be goverened by kinetics, (**3a**) being isomerized into (**4a**) on being warmed in acetic acid. The ratio [(**3a**)]:[(**4a**)] in the different solvents was carefully analysed by h.p.l.c. with a reproducibility of 0.5% (see the Experimental section for details) and was found to be a function of the solvent. The yield of the *cis* isomer (**3a**) roughly correlated with an increase in the solvent AN and, in alcohols, (**4a**) became negligible (Table 3).

These data can be rationalized by assuming the solvent is acting as an electrophile towards the heterodiene (**1a**). The effect of protonation of acrylaldehyde[12] can be used as a model. This not only lowers the acrylaldehyde LUMO, but also increases its coefficient at C-1. CNDO/2 calculations on protonated 4-benzylidene-1-phenylpyrazol-5-one provided the same result. Protonation of the oxygen atom is favoured over N-2 protonation by *ca.* 15 kcal mol^{-1}, the LUMO is strongly stabilized, and a significant increase in the LUMO coefficient at pyrazolone C-5 is observed (Figure 3). Since the non-bonding interaction that stabilizes the *endo* transition state involves the C-5 coefficient of the pyrazolone LUMO and the oxygen coefficient of the vinyl ether HOMO, the stronger the electrophile co-ordinated to the carbonyl group the greater the stabilization of the *endo* transition state, thus the lower the activation energy leading to (**3**). The significant co-ordination of the vinyl ether, which reduces the HOMO coefficient of the oxygen atom, could be the reason for the lower selectivity of the reaction in methanol and ethanol. In order to test quantitatively the effect of the solvent on stereoselectivity, we needed to know the solvent effect on a reaction with a low free-energy difference between *endo* and *exo* transition states; this would enable minimization of the error involved in the determination of adduct distribution.

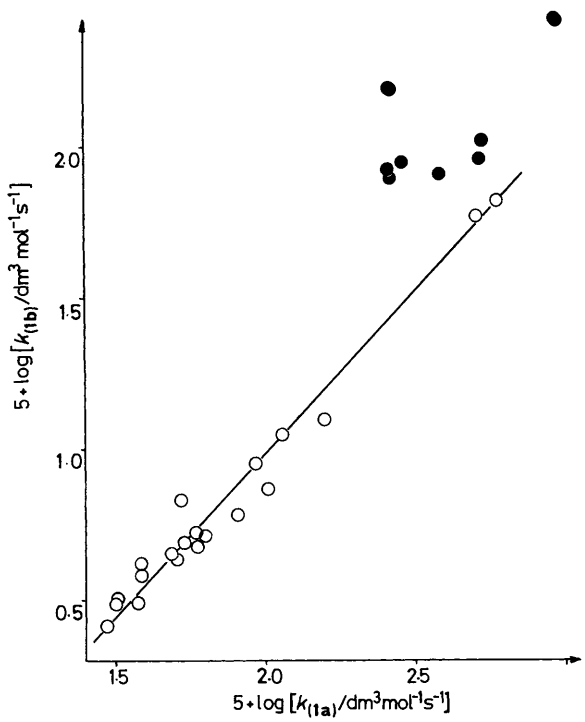


Figure 2. Plot of the rate constants for the reaction of (**1a**) and (**2**) *vs.* those for the reaction of (**1b**) and (**2**), in different solvents. Linear relationship [primary and secondary alcohols (●) excluded: ρ 1.03, intercept −1.09, and r 0.986].

* Assuming firstly that both reagents are involved in the solvation, the frontier term of the perturbation equation, with the numerator assumed as a constant, reduces to equation (2). Simple molecular

$$\Delta E = \frac{A}{E^{\text{solvated vinyl ether}}_{\text{HOMO}} - E^{\text{solvated pyrazolone}}_{\text{LUMO}}} \quad (2)$$

orbital reasoning, similar to that developed in the previous paper,[2] suggests a transformation of equation (2) into equation (3) (f, g, h, and i being constants). Equation (3), applied to primary and secondary

$$\frac{1}{\Delta E} = f\left(\frac{1}{g-\text{AN}}\right) - h\left(\frac{1}{i-\text{AN}}\right) \quad (3)$$

alcohols, has a graphic representation in accordance with the experimental data.

Table 3. Products from the reaction of (**1a**) with (**2**) in different solvents.

Solvent[a]	AN	(**3a**) (%)	(**4a**) (%)
Cyclohexane	0	92	8
Mesitylene	—	92	8
p-Xylene	—	90.5	9.5
Toluene	—	91	9
Benzene	8.2	90	10
Carbon tetrachloride	8.6	92.5	7.5
Ethyl acetate	9.3	94	6
1,4-Dioxane	10.8	92	8
Acetone	12.5	94.5	5.5
Acetonitrile	18.9	95	5
Chloroform	23.1	95	5
t-Pentyl alcohol	(27)	99.5	0.5
t-Butyl alcohol	27.1	99.5	0.5
Cyclohexanol	(31.5)	99.5	0.5
s-Butyl alcohol	(32.5)	99.5	0.5
Isopropyl alcohol	33.8	99.5	0.5
Butyl alcohol	37.3	99.5	0.5
Ethanol	37.9	99	1
Methanol	41.3	98.5	1.5

[a] The solvents not reported interfere with the h.p.l.c. analysis.

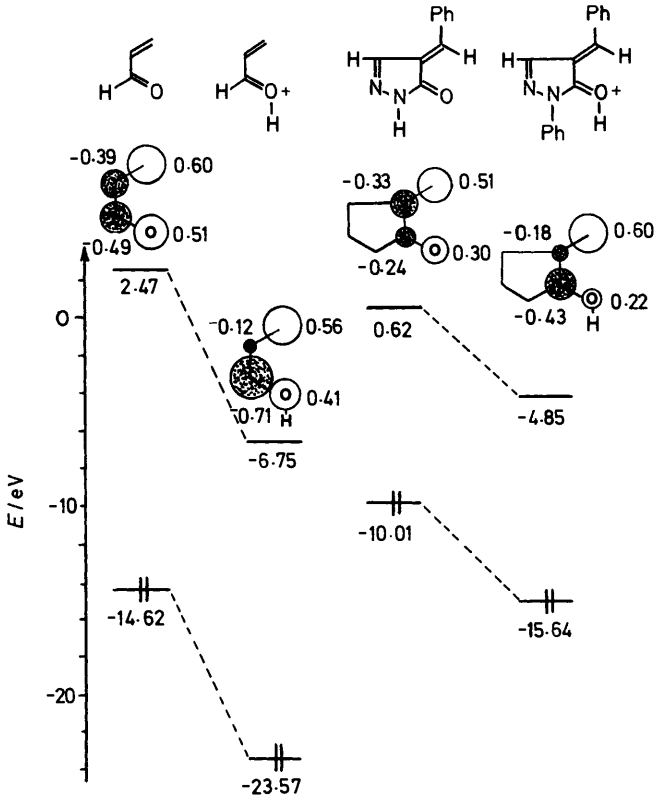


Figure 3. FMOs of protonated acrylaldehyde[12] and protonated 4-benzylidene-1-phenylpyrazol-5-one.

The literature reports the solvent effect of the DA reaction, with direct electron demand, of cyclopentadiene (**5**) with methyl acrylate (**6a**), methyl methacrylate (**6b**), and methyl *trans*-crotonate (**6c**).[13] Accurate analysis by g.c. allowed determination of the reaction mixture composition for *endo* and *exo* adducts [(**7a,c**) and (**8a,c**), respectively] (Scheme 2). The ratios for triethylamine *vs.* acetic acid (the solvents with maximum effect) were 76.3:23.7 *vs.* 88.1:11.9 for [(**7a**)]:[(**8a**)]; 22.9:77.1 *vs.* 35.9:64.1 for [(**7b**)]:[(**8b**)], and 51.2:48.8 *vs.* 70.3:29.7 for [(**7c**)]:[(**8c**)]. The log {[(**7a**)]/[(**8a**)]} values, at a given temperature, gave the solvent parameters Ω_T. The logarithms of the ratios [(**7b**)]:[(**8b**)] and [(**7c**)]:[(**8c**)] were found to be linearly related to Ω_T. Thus the solvent effect of these DA reactions was rationalized in terms of an interaction between the permanent dipoles of the diene and dienophile.[13] We used the homogeneous data of the ratios [(**7**)]:[(**8**)] at the lowest temperature (3 °C) and their logarithms were plotted *vs.* AN (Figure 4).

The correlations obtained can be explained in terms of an electrophilic interaction between solvent and dienophile (**6**), the co-ordination of solvent with cyclopentadiene being negligible. Since the entropy can be taken as constant,[13] log{[(**7**)]/[(**8**)]} is directly proportional to the difference between the activation enthalpies of *endo* and *exo* transition states, respectively. This difference is the stabilization energy arising from the non-bonding interaction between the HOMO coefficient of the cyclopentadiene C-2 (which is a constant) and the LUMO coefficient of the carbonyl carbon atom of the solvated dienophile.

Electrophiles co-ordinate to methyl acrylate at the carbonyl oxygen atom[14] and the LUMO coefficient of the carbonyl carbon atom is increased. The linear relationship between log {[(**7**)]/[(**8**)]} and the AN can be explained if it is assumed that the stronger the electrophile, then the greater the resulting effect.

Conclusions

The results suggest that the solvent plays an important role in DA reactions with either direct or inverse electron demand. It can be used not only to increase the rate by a factor comparable to that induced by the choice of an appropriate substituent, but also to induce a significant change of stereoselectivity. This may be predicted, assuming the solvent to behave as an electrophile that can co-ordinate with either the diene or the dienophile, or with both depending on their MO characteristics.

Experimental

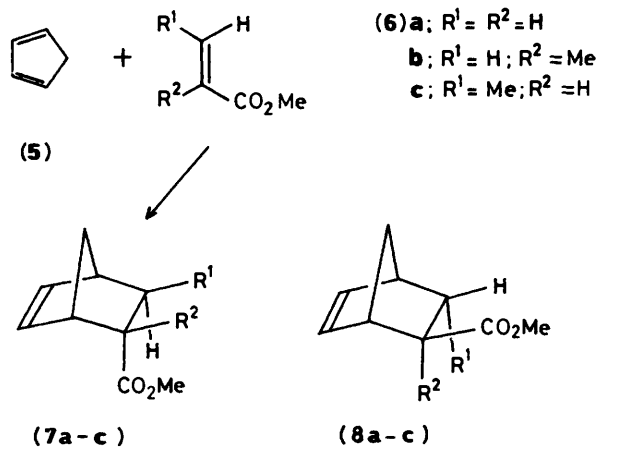
General.—Melting points were determined by the capillary method on a Tottoli apparatus (Büchi). Elemental analyses were carried out with a Carlo Erba model 1106 CHN analyser. ^{1}H N.m.r. spectra were recorded on a Bruker WP 80SY spectrometer using $CDCl_3$ as the solvent and tetramethylsilane as the standard.

Materials.—Isobutyl vinyl ether supplied by Aldrich was redistilled.

4-(p-*Nitro*)*benzylidene*-1-*phenylpyrazol*-5-*one* (**1a**).—This was prepared as reported in the literature.[7]

4-(o-*Methoxy*)*benzylidene*-1-*phenylpyrazol*-5-*one* (**1b**).—This was prepared from *o*-methoxybenzaldehyde and 1-phenylpyrazol-5-one following the method reported in the literature[7] for (**1a**): orange needles, m.p. 133 °C (from ethyl acetate) (Found: C, 73.4; H, 4.9; N, 10.0. $C_{17}H_{14}N_2O_2$ requires C, 73.4; H, 5.1; N, 10.1%).

Reaction of (**1a**) *with* (**2**).—Compound (**1a**) (0.58 g, 2 mmol) was heated to 75 °C in a sealed tube with an excess of the vinyl ether (**2**) (*ca.* 6 cm^3) until the starting colour had disappeared. On being cooled, the excess vinyl ether was removed by distillation and the residue was crystallized from ethanol. Compound (**3a**) separated as colourless crystals (0.55 g, 70%), m.p. 146–147 °C (Found: C, 66.8; H, 5.9; N, 10.8. Calc. for $C_{22}H_{23}N_3O_4$: C, 67.2; H, 5.9; N, 10.7%); δ(isobutoxy group) 0.76 and 0.78 (3 H + 3 H, d + d, *J* 7 Hz), 1.7 (1 H, m), and 3.34



Scheme 2.

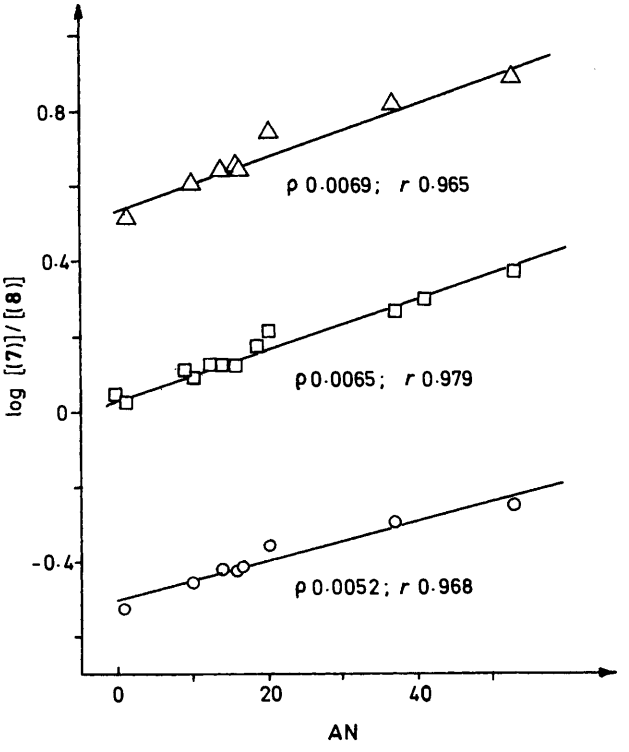


Figure 4. Linear correlation of AN *vs.* the stereoselectivity of the DA reactions of cyclopentadiene with methyl acrylate (△), methyl metacrylate (○) and methyl *trans*-crotonate (□) {the data of log [(**7**)/(**8**)] are taken from ref. 13}.

and 3.67 (1 H + 1 H, dd + dd, J 6.5 and 9.3 Hz); δ(dihydropyran) 5.40 (1 H, dd, $J_{5,6}$ 5.6, $J_{5',6}$ 2.5 Hz, 6-H), 4.26 (1 H, dd, $J_{4,5}$ 6.9, $J_{4,5'}$ 6.1 Hz, 4-H), and 2.13 and 2.43 (1 H + 1 H, $-J_{5,5'}$ 14.0 Hz, 5-H and 5'-H, respectively).

The ethanolic mother liquors were evaporated and the residue was column chromatographed [Merck silica gel 230–400 mesh, eluant: cyclohexane–ethyl acetate (9:1)]. The first fraction gave (**4a**) as an oil (0.08 g, 10%) which on crystallization from light petroleum yielded white crystals, m.p. 93 °C (Found: C, 67.1; H, 5.9; N, 10.7. $C_{22}H_{23}N_3O_4$ requires C, 67.2; H, 5.9; N, 10.7%); δ(isobutoxy group) 0.85 and 0.88 (3 H + 3 H, d + d, J 7 Hz), 1.7 (1 H, m), and 3.45 and 3.64 (1 H + 1 H, dd + dd, J 6.5 and 9.3 Hz); δ(dihydropyran protons) 5.50 (1 H, t, $J_{5,6}$ 2.2, $J_{5',6}$ 2.2 Hz, 6-H), 4.33 (1 H, dd, $J_{4,5}$ 11.0, $J_{4,5'}$ 5.8 Hz, 4-H), and 1.93 and 2.33 (1 H + 1 H, $-J_{5,5'}$ 13.8 Hz, 5-H and 5'-H, respectively). After elution of this product, a second crop of (**3a**) was isolated [total yield of (**3a**) 85%].

Reaction of (**1b**) *with* (**2**).—Compound (**1b**) (0.28 g, 1 mmol) was heated to 75 °C in a sealed tube with an excess of vinyl ether (**2**) (*ca.* 3 cm³) for *ca.* 8 h until the starting colour disappeared. After being cooled, the excess vinyl ether was removed by evaporation and the oily residue of (**3b**) (nearly quantitative yield) was purified by distillation on a cold finger, b.p. *ca.* 175 °C, 0.001 mmHg (Found: C, 73.0; H, 7.2; N, 7.4. $C_{23}H_{26}N_2O_3$ requires C, 73.0; H, 6.9; N, 7.4%); δ(isobutoxy group) 0.87 (6 H, d, J 7 Hz), 1.7 (1 H, m), and 3.37 and 3.72 (1 H + 1 H, dd + dd, J 6.5 and 9.3 Hz); δ(dihydropyran protons) 5.41 (1 H, dd, $J_{5,6}$ 7.0, $J_{5',6}$ 2.3 Hz, 6-H), 4.57 (1 H, dd, $J_{4,5}$ 8.3, $J_{4,5'}$ 6.6 Hz, 4-H), and 2.08 and 2.42 (1 H + 1 H, $-J_{5,5'}$ 14.2 Hz, 5-H and 5'-H respectively); δ 3.88 (3 H, s, OMe).

Acetic Acid-catalysed Isomerization of (**3a**).—The minor isomer (**4a**) can be prepared in significant quantity. Compound (**3a**) (0.13 g, 0.33 mmol) was heated to 100 °C for 4 h with acetic acid (5 cm³). The acetic acid was removed by distillation and the residue was found to be compounds (**3a**) and (**4a**) in the ratio *ca.* 1:4; they were separated as described above.

Solvents.—Solvents for the kinetic runs were freshly distilled reagent grade (u.v. spectroscopic grade when available).

Kinetics.—The overall reaction rates were measured by following the disappearance of (**1a,b**) on a Perkin-Elmer Lambda 5 spectrophotometer provided with a thermostatted-cell transport assembly and an automatic multicell programmer. The solutions were measured in 1.00 cm OS Hellma cuvettes of 3 cm³ capacity.

Measurements were taken at wavelengths of 454 nm for (**1a**) in aromatic solvents, acetone, nitromethane, and nitroethane, and 329 nm for other solvents (kinetic runs in dioxane and ethyl acetate at both 329 and 454 nm gave the same rate constant); 425 nm for (**1b**) in all solvents. A sample of pyrazolone (**1**) (2–3 mg) was weighed accurately and dissolved in the required solvent in a 25 cm³ volumetric flask. Isobutyl vinyl ether (**2**) (*ca.* 1–2 cm³) was poured into an accurately weighed 10 cm³ volumetric flask containing *ca.* 5 cm³ of the required solvent. On addition of (**2**), the flask was again weighed to determine accurately the amount of vinyl ether and then filled with solvent. Six samples of the solution of (**1**) (2.00 cm³ measured using a pipette) were placed in six thermostatted cuvettes and variable amounts (from 0.2–0.9 cm³, accurately measured with a microsyringe) of the solution of (**2**) were added. After vigorous mixing the kinetic determination was initiated.

In order to measure the activation parameters, the kinetic determinations at four different temperatures were performed. The rates at 20, 25, and 30 °C were determined as above and the temperature was adjusted by means of the thermostat. For the determination of the rates at higher temperatures, a solution of (**2**) (5.00 cm³) was added to the half-filled volumetric flask containing (**1b**) dissolved in the solvent and solvent was then added up to 25 cm³. Portions (*ca.* 3 cm³) of the homogeneous solution were placed into quartz tubes which were sealed. Approximately seven samples were prepared for each run. At $t = 0$ the samples were placed into a ultrathermostat at the required temperature and the absorbance of the solution was determined for a further sample. At appropriate time intervals (15–100 min) the reaction was quenched using ice and the residual absorbance of (**1b**) was determined.

Determination of the [(**3a**)]:[(**4a**)] *Ratio.*—This was performed by h.p.l.c. on a Waters Associated ALC/CPC 244 liquid chromatograph with a Beckman mod. 25 spectrophotometer

operating at 255 nm as the detector. The chromatographic separation was performed on a stainless steel column (61 cm length × 2 mm diam.), packing material: Corasil I 37–50 μm; eluant: cyclohexane–ethyl acetate 95:5, flow 1.2 cm^3 min^{-1}, retention times: (**4a**) 3.7, (**3a**) 8.5 min. Six solutions of known composition of pure (**3a**) and (**4a**) were prepared with [(**3a**)]:[(**4a**)] = 80:20–98:2, each composition being tested on two independent samples at least four times each. A calibration curve was thus obtained and the unknown compositions were determined by fitting the ratio of the peak heights to it. In a sealed quartz tube compounds (**1a**) (3 mg), (**2**) (0.3 cm^3) and solvent (5 cm^3) were heated to 35.7 °C until the colour of the solution had disappeared. The majority of the solvent was removed under vacuum at room temperature and the residue was dissolved in a small volume of eluant. Each solvent was tested on three independent samples at least four times each.

The reaction mixtures of several solvents were tested at different degrees of completion and the ratio [(**3a**)]:[(**4a**)] was found to be constant within the limits of experimental error.

Acknowledgements

The authors are grateful to Professor A. Rastelli (Modena) for helpful discussions and to National Research Council (CNR) and M.P.I. for financial support.

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Received 15*th February* 1988; *Paper* 8/00631H